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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/412,558	10/05/1999	JUALANG HWANG	08919/022001	9802

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EXAMINER
DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
1645	17

DATE MAILED: 03/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/412,558	Hwang et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 10, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *14, 15, 17, 18, and 24-27* is/~~are~~ pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *14, 15, 17, 18, and 24-27* is/~~are~~ rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Dec 10, 2002* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendments

1) Acknowledgment is made of Applicants' amendments filed 12/10/02 (paper no. 13) in response to the Office Action mailed 06/05/02 (paper no. 10).

Status of Claims

2) Claims 1-13, 16 and 19-23 have been canceled via the amendment filed 12/10/02.

Claims 14, 15, 17 and 18 have been amended via the amendment filed 12/10/02.

New claims 24-27 have been added via the amendment filed 12/10/02.

Claims 14, 15, 17, 18 and 24-27 are pending and are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

5) The objection to the drawings made in paragraph 6 of the Office Action mailed 06/05/02 (paper no. 10) is withdrawn in light of Applicants' submission of corrected drawings which have been approved by the Draftsperson.

Rejection(s) Withdrawn

6) The rejection pf claims 14, 15 and 17 made in paragraph 7(a) of the Office Action mailed 06/05/02 (paper no. 10) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' explanation.

7) The rejection pf claims 14, 15, 17 and 18 made in paragraph 7(b) of the Office Action mailed 06/05/02 (paper no. 10) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

8) The rejection pf claims 14, 17 and 18 made in paragraph 11 of the Office Action mailed 06/05/02 (paper no. 10) under 35 U.S.C. § 102(b) as being anticipated by Hwang *et al.* (*Cell* 48: 129-136, 1987 - Applicants' IDS) (Hwang *et al.*, 1987) or Hwang *et al.* (*J. Biol. Chem.* 264: 2379-

2384, 1989 - Applicants' IDS) (Hwang *et al.*, 1989), is withdrawn in light of Applicants amendment to the claims and/or the base claim(s).

9) The rejection pf claims 14, 15 and 18 made in paragraph 10 of the Office Action mailed 06/05/02 (paper no. 10) under 35 U.S.C. § 102(b) as being anticipated by Hickey *et al.* (WO 97/15325), is withdrawn in light of Applicants amendment to the claims and/or the base claim(s).

10) The rejection pf claims 14, 15, 17 and 18 made in paragraph 13 of the Office Action mailed 06/05/02 (paper no. 10) under 35 U.S.C. § 103(a) as being unpatentable over Potter *et al.* (WO 96/24675, published 15 August 1996) Russell-Jones *et al.* (WO 91/02799) in view of Hwang *et al.* (*J. Biol. Chem.* 264: 2379-2384, 1989 - Applicants' IDS) (Hwang *et al.*, 1989) and Pastan *et al.* (Us 4,892,827), is withdrawn in light of Applicants amendment to the claims and/or the base claim(s).

Rejection(s) under 35 U.S.C. § 112, First Paragraph

11) Claims 24-27 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Instant claims include the limitation: "nucleic acid ..... excludes the non-receptor binding domain of the *Pseudomonas* exotoxin A". Applicants point to page 1, lines 21-24 and page 9, line 6 through page 13, line 13 as providing descriptive support for the limitation. However, this part of the specification does not provide descriptive support for the negative/exclusive limitation identified above. Therefore, the above-identified limitations in the claims are considered to be new matter. An amendment to a claim must have support in the original disclosure. MPEP 2163.06 states that Applicants should specifically point out the support for any amendments made to the disclosure. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P. 608.04 to 608.04(c).

Applicants are invited to point to the descriptive support in specific part(s) of the disclosure, as originally filed, for the limitation identified above, or to remove the new matter from the claims and/or the base claim(s).

Rejection(s) under 35 U.S.C. § 102

12) Claims 14 and 18 are rejected under 35 U.S.C. § 102(e) as being anticipated by Lorberboum-Galski *et al.* (US 6,140,066, filed 24 March 1998, already of record) as evidenced by Burnie *et al.* (EP 0 406 029).

The transitional limitation "comprises" similar to the limitations such as, "has", "includes," "contains," or "characterized by," represents open-ended claim language and therefore does not exclude additional, unrecited elements. See M.P.E.P 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts"). On the other hand, the limitation "consisting of" represents closed claim language and excludes any element, step, or ingredient not specified in the claim. *In re Gray, 53 F.2d 520, 11 USPQ 255 (CCPA 1931)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948).*

Lorberboum-Galski *et al.* disclose a DNA sequence encoding a polypeptide comprising a full length *Pseudomonas* exotoxin A (PE) and copies or repeats of a peptide sequence, gly-gly-gly-gly-ser, in a consecutive series (see Figure 1; 'Brief Description' for Figure 1; first full paragraph under 'EXAMPLE'; and column 10, lines 42-45). The peptide sequence is repeated three times (see last paragraph in column 2). That the prior art full length *Pseudomonas* exotoxin A 'comprises' a receptor binding domain of *Pseudomonas* exotoxin A is inherent from the teachings of Lorberboum-Galski *et al.* That the prior art 5 amino acid-long peptide sequence, gly-gly-gly-gly-ser, serves as an antigen is inherent from the teachings of Lorberboum-Galski *et al.* in light of what is well known in the art. For instance, Burnie *et al.* disclosed that a peptide consisting of five amino acids serves as an epitope (see last paragraph on page 3).

Claims 14 and 18 are anticipated by Lorberboum-Galski *et al.* Burnie *et al.* is **not** used as a secondary reference in combination with Lorberboum-Galski *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Lorberboum-Galski *et al.* See *In re Samour* 197 USPQ 1 (CCPA 1978).

13) Claims 14-18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hickey *et al.* (WO 97/15325 - already of record).

The transitional limitation "comprises" similar to the limitations such as, "has", "includes," "contains," or "characterized by," represents open-ended claim language and therefore does not exclude additional, unrecited elements. See M.P.E.P 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts"). On the other hand, the limitation "consisting of" represents closed claim language and excludes any element, step, or ingredient not specified in the claim. *In re Gray, 53 F.2d 520, 11 USPQ 255 (CCPA 1931)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948).*

Hickey *et al.* teach GnRH-PE chimeric hybrid proteins produced by recombinant DNA technology (see third full paragraph on page 6; second full paragraph on page 7; page 12, third full paragraph; and last paragraph on page 10). The GnRH peptide has the amino acid sequence of SEQ ID NO: 1 (see second full paragraph on page 8). The hybrid proteins contain contiguous sequences of the constituent proteins/peptides and are preferably manufactured through expression of recombinant DNA sequences (see page 29, second full paragraph). The hybrid GnRH protein manufactured by recombinant DNA techniques comprises as many as 2 to 20 native GnRH molecules (see page 13, especially the formula wherein X is GnRH and r is 1 to 10). The recombinant DNA encoding the hybrid proteins of the invention are taught on page 20, 21, 29 and 30.

Claims 14-18 are anticipated by Hickey *et al.*

Rejection(s) under 35 U.S.C. § 103

14) Claims 24-27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hickey *et al.* (WO 97/15325 - already of record) in view of Hwang *et al.* (*J. Biol. Chem.* 264: 2379-2384, 1989 - Applicants' IDS) (Hwang *et al.*, 1989) and Pastan *et al.* (US 4,892,827 - already of record).

The disclosure of Hickey *et al.* is described above which teaches a nucleic acid encoding a polypeptide comprising at least two copies of the antigenic peptide sequence of SEQ ID NO: 1 fused to a *Pseudomonas* exotoxin A, but not the exotoxin A wherein the non-receptor binding domain is excluded.

However, the use of *Pseudomonas* exotoxin consisting of the receptor binding domain Ia for

vaccination or *in vivo* administration has been suggested in the art. For example, Hwang *et al.* (1989) taught a nucleic acid sequence encoding domain Ia of PE. Hwang *et al.* expressly taught that domain Ia of PE can be used for vaccination purposes (see right column on page 2379).

Similarly, Pastan *et al.* taught recombinant gene fusions using PE (see column 6, lines 30 and 31) and the pJH14 plasmid that encodes structural domain Ia of PE comprising amino acids 1-252 (see column 6, lines 60 and 61). Pastan *et al.* taught that domain Ia of PE exhibits greatly diminished toxicity in mice (see column 6, lines 21, 22, 27 and 28). Pastan *et al.* expressly taught the fusion of PE or part of PE with other polypeptides, including luteinizing hormone (see column 6, lines 36-43). Pastan *et al.* specifically taught that the protein encoded by domain I could be administered for treatment purpose, because it would block toxin binding to cells (see column 1, lines 15-18). Thus, both Hwang *et al.* (1989). Thus, Pastan *et al.* taught the suitability of domain Ia of PE for *in vivo* administration, and its advantageous properties, such as, greatly diminished toxicity and the ability to block toxin binding to cells.

Hickey *et al.* further taught that a variant of *Pseudomonas* exotoxin can also be used in the hybrid construct (see page 7; and claims). One of skill in the art would understand that Hwang's or Pastan's domain Ia of PE serves as a variant of *Pseudomonas* exotoxin.

Given the express teaching of Hwang *et al.* (1989) that domain Ia of PE can be used for vaccination purposes and Hickey's explicit teaching that a variant of PE can be used in their GnRH-PE chimeric hybrid protein construct, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace the nucleic acid encoding the whole PE in Hickey's fusion construct with Pastan's or Hwang's nucleic acid sequence encoding only domain Ia of PE, to produce the nucleic acid of the instant invention, with a reasonable expectation of success, because Pastan *et al.* expressly taught that fusion can be performed with a luteinizing hormone and a part of PE, and Hickey *et al.* expressly taught that a variant of PE can be used in their GnRH-PE chimeric hybrid protein construct. Given the explicit teaching by Hickey *et al.* that a variant of PE can be used in their GnRH-PE chimeric hybrid protein construct, one of skill in the art would have been motivated to produce the instant invention for the expected benefit of blocking the toxin binding to cells and providing a PE variant that has greatly diminished toxicity, because Pastan *et al.* explicitly taught that the protein encoded by domain I of PE could be administered for

therapeutic purpose and that it is of greatly diminished toxicity and would advantageously block toxin binding to cells.

Claims 24-27 are *prima facie* obvious over the prior art of record.

Pertinent Prior Art

15) The prior art made of record and not relied upon currently in any of the rejections are considered pertinent to Applicants' disclosure.

- Russell-Jones *et al.* (WO 91/02799)) expressly taught that insertion of tandem repeats of LHRH analogues (i.e., peptide sequences) gives more immunogenic fusion than the insertion of a single insert (see page 6, lines 26-29). Russell-Jones *et al.* expressly taught the use in fusion constructs of four and eight LHRH analogue inserts (see page 29, lines 4-6; page 21, lines 1-7; and Figure 5). Russell-Jones *et al.* explicitly taught that multiple inserts of LHRH analogue were consistently more immunogenic evoking a higher anti-LHRH response than constructs containing a single insert (see page 29, lines 26-29). Russell-Jones *et al.* demonstrated that an increase in LHRH antibody levels in dogs corresponded to an increase in the LHRH analogue units in the fusion protein construct and concluded that the introduction of multiple copies of the peptide in the fusion construct considerably enhances the immunogenicity of the inserted peptide (see page 30, lines 4-10).

Remarks

16) Claims 14, 15, 17, 18 and 24-27 stand rejected.

17) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory

period for reply expire later than SIX MONTHS from the mailing date of this final action.

18) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

19) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached at (703) 308-3909.

March, 2003

S. DEVI, PH.D.
PRIMARY EXAMINER